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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,700	03/13/2002	Edwin L. Madison	24745-1613	4309

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FISH & RICHARDSON, PC
12390 EL CAMINO REAL
SAN DIEGO, CA 92130-2081

EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/099,700	MADISON ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8-10,18,19,50-55,59-61,65-67 and 69-122* is/are pending in the application.

4a) Of the above claim(s) *73-116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-10,18,19,50-55,59-61,65-67,69-72 and 117-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050209*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection on 9 February 2005. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9 February 2005 has been entered.

Response to Amendment

Applicant's Amendment filed 9 February 2005, has been entered, amending claims 4, 18, 65, and 69. Non-elected claims 73-116 remain in the application and, in the event of rejoinder, any rejoined process claim must meet the requirements of 35 U.S.C. §§ 101, 102, 103, and 112 even though the restriction requirement between the product claims and non-elected process claims be withdrawn. Claims 1, 2, 4-6, 8-10, 18, 19, 50-55, 59-61, 65-67, and 69-122 remain herein and claims 73-116 are withdrawn from consideration as drawn to non-elected inventions.

Claim Rejections – Utility - 35 USC § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 65-67 and 69-72 remain rejected for reasons of record under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

Applicant's arguments at pages 13-17 of the Response filed 9 February 2005 have been fully considered but are not persuasive in establishing that the recitation, "and the identified compounds inhibit tumorigenesis", added to amended claims 65 and 69 can confer a specific and substantial utility on claimed methods of using a MTSP7 protease

to identify "modulators". The utility of a claimed method depends upon disclosure of a specific and substantial utility for a compound discovered, but there is no teaching of what an undisclosed compound detected by a claimed method "modulates", i.e., there is no specific or substantial utility for the "modulator", whether it inhibits or enhances protease activity. Four appellate decisions cited at pages 14 and 15 of the Response are not relevant, three because they concern no method, but instead concern the utility of a disclosed compound or machine, and the fourth concerns utility of a therapeutic method of treatment[1] using a compound. One decision cited in the Response, *Hoffman v. Klaus*[2], is relevant to arguments made in the Response but does not support them. *Hoffman* took up the issue of a relationship between utility of a compound disclosed in an application for patent and a method of identification involving the compound. The Board found that the party failed to show that screening tests, tests that were actually conducted rather than hypothetical tests, for compounds to inhibit arthritis were sufficient under *Nelson v. Bowler*, 206 USPQ 881, to qualify as "practical utility," in view of the lack of evidence that one skilled in art would have been reasonably certain that the compound of the count had practical utility at time the tests were performed. No evidence demonstrated a correlation between the *in vitro* tests, in which the compound inhibited production of collagenase, and the treatment of arthritis or any other useful purpose. By contrast, the instant specification discloses no specific and substantial utility for any compound discovered by a claimed method. The Response establishes no nexus between a proposed differential expression of an MTSP7 protease, which is

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[1] *In re Gottlieb*, 140 USPQ 665 (CCPA 1964), a claimed antibiotic, "filipin". *Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983), a microwave oven. *In re Malachowski*, 189 USPQ 432 (CCPA 1976), a composition comprising anthracite coal residue and methods of treating arthritis. *In re Gazave*, 154 USPQ 91 (CCPA 1967), methods of treatment utilizing a particular isoflavone.

[2] 9 USPQ2d 1657 (Bd. Pat. App. & Int. 1988).

not demonstrated in the specification, and the process of "tumorigenesis" which is argued to provide utility for a claimed method to find a "modulator".

The Response suggests that pages 2, 4, 11, 47, and 70-71 of the specification are a basis for the amended claims in that that they might disclose a "modulator" detected by a method that will also inhibit tumorigenesis. The term "modulator" is construed to describe a compound that may either augment or inhibit MTSP7 protease activity. But the term "tumorigenesis" is not present at any of the cited pages of the specification and the portions of the specification quoted at page 16 of the Response and the paragraph spanning pages 71 and 72 of the specification do not disclose that a "modulator" of a MTSP7 protease will inhibit tumor growth by affecting a process the Response argues at pages 15 and 16. The Response points to pages 86-87 of the specification that propose *in vivo* testing of compounds for activity against tumor cell lines after surgically implantation in test animals such as SCID mice. The word "tumorigenesis" does not occur at pages 86-87 and the rejected claims do not describe the hypothetical *in vivo* tests of the specification. The specification discloses a specific and substantial utility for a native MTSP7 **protease**, cleavage of the specific, artificial, peptide substrate, S2366, but disclosure of a single substrate for assay of MTSP7 protease activity cannot confer utility on methods for identifying a "modulator" where the nature of the utility sought in the claim amendment is not set forth in the specification. The rejection of record is sustained because the specification provides no nexus showing how the protease might be, or might not be, associated with any disease or physiological condition.

Claim Rejections - Enablement as to Use - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65-67 and 69-72 also remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, for lack of enablement as to use.

The Response does not separately argue that the rejection of record of claims 65-67 and 69-72 under 35 U.S.C. § 112, first paragraph, for lack of enablement as to use fails because it is based on an improper rejection of record under 35 U.S.C. § 101 for lack of patentable utility of claims 65-67 and 69-72. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed methods. The rejection of record is therefore sustained.

Claim Rejections - New Matter and Written Description- 35 USC § 112

Claims 1, 2, 4-6, 10, 18, 19, 50-55, 59-61, 65-67, 69-72, and 117-122 remain rejected essentially for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 4, 6, 52-54, 65-67 and 69-72 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because the amendments to claims 4, 65 and 69 filed 9 February 2005 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, there is no disclosure of a polypeptide comprising "an MTSP7 portion" that is "the only MTSP7 portion" of the polypeptide, or of a conjugate that comprises such a polypeptide, and there is no disclosure that a method of claims 65-67 and 69-72 identifies a "modulator" that will "inhibit tumorigenesis", thus Applicant's amendments necessitates this new ground of rejection. The use of the term "only" at pages 20, 28, 29, 37, and 64 of the specification does not support a recitation of "said MTSP7 portion is the only MTSP7 portion" of a polypeptide of claim 4 which

excludes, without basis in the specification, [3] a second "portion" of a polypeptide that corresponds to a "portion" of some other polypeptide that somehow differs from a first indicated "portion" of a MTSP7 polypeptide. As noted above in the rejection for lack of specific and substantial utility, "tumorigenesis" is not present at any of the cited pages of the specification, including pages 86-87 of the specification.

Applicant's arguments at pages 17-27 of the Response filed 9 February 2005 concerning the rejection of record have been fully considered but are not persuasive. The subject matters that necessitate maintaining the rejection of record are reviewed before taking up the arguments in the Response.

A. The independent claim 119 and clause (a) of independent claim 1 reach polypeptides with amino acid sequences that diverge as much as 10% from the integral MTSP7 amino acid sequence set forth in SEQ ID NO:16. Such divergence may be any of all of amino acid deletions, insertions, or substitutions anywhere, in any pattern or combination throughout the length of SEQ ID NO:16. The Response does not dispute that clause (a) of claim 1 is intended to reach polypeptides differing at as many as 44 amino acid positions from the amino acid sequence of SEQ ID NO:16. Claims 2, 5, 10, 18, 19, 50, 51, 59-61, 65-67, and 70-72 are included in this rejection because they depend from, or refer to, claim 1 but state no other significant structural limitation. Clause (b) of claim 1, however, reaches polypeptides with amino acid sequences that diverge much more than 10% from that of SEQ ID NO:16 since the limitation, "a polypeptide that comprises a sequence of amino acids encoded by" the nucleic acid

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[3] Page 20 teaches that a "recitation that a polypeptide consists essentially of the protease domain means that the only MTSP portion of the polypeptide is a protease domain or a catalytically active portion thereof" and page 64 discusses, by comparison, a "polypeptide that . . . contains all or a portion of only the protease domain . . . of an MTSP protein". Neither definition excludes an amino acid beyond the boundaries of SEQ ID NO:18 that is, in some part, a variant of clause (b) of claim 4.

sequence of SEQ ID NO:15, is satisfied by a polypeptide retaining no more than a di- or tripeptide sequence of SEQ ID NO:16. This communication addresses the arguments in the Response to the extent that they pertain to clause (a), rather than clause (b), of claim 1, because amending clause (a) may overcome the rejection of record whereas clause (b), which is also ambiguous, must be deleted to overcome the rejection.

B. Independent claim 120 and clause (b) of independent claim 4 reach polypeptides having amino acid sequences that diverge as much as 10% from the MTSP7 catalytic domain amino acid sequence set forth in SEQ ID NO:18. Such divergence may be any of all of amino acid deletions, insertions, or substitutions anywhere, in any pattern or combination throughout the length of SEQ ID NO:18. The Response does not dispute that clause (b) of claim 4 reaches polypeptides differing at as many as 23 amino acid positions from the amino acid sequence of SEQ ID NO:18. Claims 6, 52-55, 69, 117 and 118 are included in this rejection because they depend from claim 4 but state no other significant structural limitation. Arguments in the Response are addressed herein as they pertain to clauses (a) and (b) of claim 4 because deficiencies of the preamble and clauses (a) and (b) of the claim may be cured by amendments that overcome both this rejection of record and the further rejection below under the second paragraph of the statute for indefinite description. Clause (c) of claim 4, however, reaches polypeptides with amino acid sequences that diverge much more than 10% from that of SEQ ID NO:18 because these polypeptides need be only a "portion" of an amino acid sequence already diverging at 10% of positions in amino acid sequence set forth in SEQ ID NO:18 identified as the MTSP7 catalytic domain. The preamble of claim 4 must be amended to remove the new matter introduced by amendment and to state an extent of modification disclosed by the specification, and clause (c) of claim 4 must be deleted, to avoid this rejection because the specification provides no adequate description of a

"catalytically active portion" of SEQ ID NO:18 that diverges from SEQ ID NO:18 as well. The Response does not dispute that clause (b) of claim 4 reaches polypeptides differing at as many as 23 amino acid positions from the amino acid sequence of SEQ ID NO:18.

C. Independent claim 121 reaches polypeptides having amino acid sequences that may diverge as much as 20% from the integral MTSP7 amino acid sequence set forth in SEQ ID NO:16. Such divergence may be any of all of amino acid deletions, insertions, or substitutions anywhere, in any pattern or combination throughout the length of SEQ ID NO:18. The Response does not dispute that clause (a) of claim 1 is intended to reach polypeptides differing at as many as 44 amino acid positions from the amino acid sequence of SEQ ID NO:16. Arguments in the Response are addressed herein as they pertain to claim 121 only to the extent that it further exceeds subject matters of claims 1 and , which already go beyond the specification's description of MTSP7 protease species the inventors possessed at the time Applicant's priority application was filed.

The Response argues at pages 20-22 that words and phrases at pages 8, 49, and 52 of the specification and in the original claim 11, e.g., "at least about 60%, 70%, 80%, 85%, 90% or 95% sequence identity" and "at least about 60%, 80%, 90% or 95% sequence identity" constitute structural definitions of undisclosed protease species. But these are no more than statistical expressions of subject matter that Applicant hopes to capture.[4] Contrary to the assertion at page 21 of the Response, the rejected claims herein do not define chemical formulas in the manner of claims to organic chemical compounds that were discussed in *Eli Lilly*, [5] i.e., claims reciting locations on a core

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[4] "Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement." *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002).

[5] 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), quotated page 21 of the Response. Claims drawn to organic chemical compounds also were addressed in the decision

structures where variations may occur and sets of permissible substituents for each location. Instead, claims rejected herein define no more than hoped-for results because neither the claims nor the specification indicate where 44, or 88, variations might occur among the 422 positions of SEQ ID NO:16 that the specification ignores, nor indicate where 23 variations might occur among the 221 positions of SEQ ID NO:16 that the specification ignores, or what the range of variations might be at any of these positions that will support a disclosed function. Claim 18 is the only claim herein identifying a particular substituent but identifies no particular site for substitution among the eight cysteines the specification discusses.

The specification discloses only two structures for a MTSP7 protease: the initial expression product having the amino acid sequence set forth in SEQ ID NO:16 and an abbreviated form having the amino acid sequence set forth in SEQ ID NO:18 which, according to the teaching at page 49, lines 7-9, of the specification, constitutes that "portion" of SEQ ID NO:16 cleaved between positions 205 and 206 of SEQ ID NO:16 to activate the protease catalytic domain. The Response suggests that subsequently-discovered proteases should be captured by the rejected claims (i) if an algorithm comparing SEQ ID NO:16 or SEQ ID NO:18 to amino acid sequences of later-discovered polypeptides detects a recited degree of statistical identity, (ii) if histidine, aspartate, and serine occur at positions similar to positions 248, 293, and 389 of SEQ ID NO:16, and (iii) if expression and recovery of the polypeptide permits a determination that it has some serine protease activity. It is agreed that each of the histidine, serine, and aspartate at, respectively, positions 248, 293, and 389 of SEQ ID NO:16 must be retained to assure serine protease activity and the Response agrees, at page 21 lines 4-6, that there can be no variation at these three sites in a MTSP7 protease.

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cited at page 24 of the Response, *In re Gosteli*, thus are distinct from the DNA claims on appeal in *Eli Lilly* and the polypeptide claims presented in the instant application.

Yet both the specification and the prior art cited in the Response, e.g., Hooper et al. and Lin et al., teach away from altering six of the cysteines forming disulfide bonds that stabilize the tertiary structures of Type II transmembrane serine protease catalytic domains. These are positions 233, 249, 358, 374, 385, and 413 of the MTSP7 amino acid sequence set forth in SEQ ID NO:16, and the specification identifies, at pages 51-52, only a single cysteine, at position 313, as suitable for an amino acid substitution. Of the sixteen amino acid positions for which the specification identifies a structural or a catalytic function in the MTSP7 protease, nine amino acid positions - the three catalytic amino acids and the six intra-domain disulfide bond-forming cysteines - must remain unaltered. The specification teaches alterations at only six of the remaining amino acid positions - Cys_{313} and the activation cleavage-site array at positions 205-209 of SEQ ID NO:16 – and discloses for each a suitable set of isofunctional amino acid substituents. The specification does not suggest that Cys_{186}, the only other position that it identifies, be altered, thus the specification affirmatively teaches modification at only 1% (six) of the amino acid positions of SEQ ID NO:16 and affirmatively teaches modification of 2% (five) of the amino acid positions present in SEQ ID NO:18.

The specification identifies very few features in the primary structure, the amino acid sequence, of the MTSP7 protease and identifies only six positions therein for alteration, but it identifies no secondary or tertiary structural features of a MTSP7 protease.[6] The Response cites *In re Gosteli*[7] pages 24 and 26 to urge that the specification need not

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[6] Contrary to suggestions at page 25 of the Response, the specification makes only passing mention of the "oxyanion hole", at page 19, and identifies no portion of SEQ IDs NOs:16 and 18 associated with this structure. The specification similarly relinquishes the determination of all other features, beyond the catalytic triad that Applicant cites at page 25, to others.

[7] 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). *Gosteli* is, however, contrary because the appellate panel sustained the lower, adverse, decision of unpatentability where Gosteli's foreign priority document failed to disclose particular species of compounds covered by the claims on appeal that had been fully disclosed in a US patent issuing on an application filed on a date intervening between filing dates of Gosteli's foreign and US applications and applied as an

identify particular locations for as many as 23, 44, or 88 modifications, or particularly identify any other structures beyond the catalytic triad, to meet the statutory requirement for an adequate written description since the state of the art can help one of skill in the art recognize how fill the considerable gap between the six positions the specification identifies for alteration and the significant amount of variation expressed statistically by the rejected claims. At page 22, the Response quotes a portion of the decision in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*[8] to support the proposition that identifying the amino acids of the catalytic triad in the single disclosed MTSP7 polypeptide satisfies the written description requirement for the myriad undisclosed species of polypeptides of the rejected claims that have a generic function of serine protease activity. But the appellate panel in *Amgen* found that "[b]oth *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." This is because the claims on appeal referred to "types of cells that can be used to produce recombinant human EPO." The *Amgen* panel also found that the district court properly concluded that "the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders *Eli Lilly* listless in this case." The *Amgen* decision is not relevant to the written description issue in the instant application because commonly-used host cells are not at issue in the claims rejected herein and

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anticipatory reference under 102(e). The appellate panel held that "the PTO has met [its] burden [of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims] by pointing out [a] number of differences between what is disclosed in the [appellant's] priority application and what is claimed in [appellant's] United States application". 872 F.2d at 1012, 10 USPQ2d 1614 at 1618.

[8] "[T]he written description requirement . . .may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known, structure . . ." 314 F.3d 1313 at 1339, 65 USPQ2d 1385 at 1399 (Fed. Cir. 2003).

the claims herein offer only a statistical description of a new member of a new class of transmembrane, i.e., cell-associated, serine proteases specifically modified or unique, molecules, and to conjugates of the generic molecules.

Central to all arguments in the Response is whether the specification's identification of the catalytic triad of amino acids within the protease domain set forth in SEQ IDs NOs:16 and 18, coupled with awareness of prior art sequence comparison algorithms and prior art modifications of serine proteases generally, would lead one of skill in the art to conclude that Applicant had invented the myriad, undisclosed, protease species that diverge at as many as 44, or 88, amino acids anywhere among the remaining 435 positions of SEQ ID NO:16, or at as many as 23 amino acid positions anywhere among the remaining 228 positions of SEQ ID NO:18. Yet neither Hooper et al. nor Lin et al., cited at pages 25 and 30 the Response, disclose or suggest any alteration of the amino acid sequences of the catalytic domain regions, or other regions, of prior art Type II transmembrane serine protease, such as the matriptase discussed by Lin et al., on the basis of sequence alignments or algorithm-based comparisons despite the fact that Lin et al. align, Fig. 4, protease domain sequences of four Type II transmembrane serine proteases and trypsin and chymotrypsin. Lu et al. and Xu et al., cited at page 30 of the Response, demonstrate why Hooper et al. and Lin et al. do not suggest or discuss modifying the amino acid sequence of a Type II transmembrane serine protease: Both Lu et al. and Xu et al. had to rely on prior crystallization of the serine proteases and X-ray diffraction analyses of the crystallized proteases to guide their selection of locations for modification. Xu et al. cite a prior report, see page 379, left column, of resolution of the serine protease domain of complement factor B "at 2.1-Å resolution [that] revealed the expected chymotrypsin fold but also unique features of surface loops and of the oxyanion hole" leading them to select five sites for amino acid substitutions, including a

joint substitution at two of the sites, see Figures 3-7, where Figure 5 shows that substitutions switching charged for uncharged amino acids, or vice-versa, at three of the five sites nearly eradicated proteolytic activity. Lu et al. began by forming a co-crystal of enterokinase, more closely related to the MTSP7 protease than the complement Factor B, complexed with an inhibitory molecule in order to determine its tertiary structure from X-ray diffraction analysis and only then proceeded with amino acid-specific chemical mutagenesis and site-directed mutagenesis affecting five amino acid positions, where a substitution at one of the positions effectively abolished, see results for K99A in Figure 9, proteolytic activity with a peptide substrate corresponding to the enterokinase native substrate. Lu et al. conclude, page 369, right column, that "an exosite", i.e., "distinct from the catalytic center", is required for recognition of the native substrate by this Type II transmembrane serine protease – see Table I of Hooper et al. – and that "at least one site on the heavy chain", a non-protease domain, "interacts with and further accelerates the cleavage" of the enterokinase native substrate, trypsinogen.

Thus, publications of Lu et al. and Xu et al. refute arguments in the Response that identification of positions of the catalytic triad together with the availability of algorithm-based amino acid sequence comparisons, combined with the disclosures in the prior art of limited amino acid sequence substitutions, might lead one of skill in the art to conclude that Applicant possessed the myriad, undisclosed, protease species diverging at as many as 44, or 88, amino acids anywhere among the remaining 435 positions of SEQ ID NO:16, or at as many as 23 amino acid positions anywhere among the remaining 228 positions of SEQ ID NO:18. Instead, Lu et al. and Xu et al. show that making a few amino acid sequence modifications in two mammalian serine proteases, one of which is Type II transmembrane serine protease, where some substitutions provide proteolytic activity and others cripple proteolytic activity requires a much more

extensive disclosure than the present specification provides: visualization of the tertiary structure of not only the protease domain but spatially proximate non-protease domains. Less relevant publications cited in the Response are those of Craik et al. and Spring et al. concerning the spatial relationship of amino acids that constitute the catalytic triad of trypsin, the prototype trypsin-like protease that is secreted into the digestive tract and activated by enteropeptidase. Both Craik et al. and Sprang et al., however, required an X-ray diffraction analysis of trypsin crystals to determine its tertiary structure and the orientation of the catalytic triad and its surrounding amino acids to each other and to the rest of the protease molecule in the tertiary structure, see pages 905-908 and Figures 1-3 of Sprang et al., and page 909, middle column, and page 912, middle column of Craik et al., in order to then determine that altering trypsin's catalytic triad by amino acid substitutions eliminates its proteolytic activity. Likewise, Nienaber et al., 2000, required X-ray diffraction analysis of crystalline urokinase to determine the three dimensional structure of native urokinase in order to then make a truncated form with two amino acid substitutions, and then made crystals of this "re-engineered form" complexed with selected inhibitors in order to visualize the orientation of the active site region with respect to its binding of inhibitors as substrates. Somerhoff et al. used X-ray diffraction analysis of mast cell tryptase crystals to determine the quarternary structure of the tetramer and the tertiary structure of each monomer in order to visualize, see Figures 1-5 and particularly Figure 3, the structure of the active site region and orientation of the oxyanion hole to the rest of the monomer.

Indeed, crystal formation and X-ray diffraction analysis were prerequisites for serine protease amino acid sequence modifications in all but two publications cited in the Response: Bachovchin et al. made no alteration of the *Lysobacter enzymogenes* α–lytic protease amino acid sequence and Cheah et al. did not need X-ray diffraction

analysis to confirm that, as previously shown for a poliovirus cysteine protease, another picornaviral protease, the rhinovirus 3C protease, also utilized cysteine in the place of serine as part of a catalytic triad. Cheah et al. show that their amino acid substitutions at positions in a catalytic triad that is aligned with the trypsin catalytic triad, "completely destroyed $3C^{pro}$ [the viral protease domain] activity".[9] Three further articles supplied with and cited in the Response, Pearson et al., Altschul et al., and Devereux et al.,, concern the use of algorithms for assessing statistical similarity without disclosing amino acid sequence modifications of a serine protease. The identification in Example 3 of the instant specification of an artificial peptide substrate, S2366, for an MTSP7 protease of SEQ IDs NOs:16 or 18 cannot support the possession of a genus of statistically-related but undisclosed MTSP7 proteases because the S2366 peptide also serves as a substrate for other proteases not be closely related in primary structure, e.g., plasmin as disclosed at page 164 of the specification, under a broad range of concentrations.

The Response also cites several articles that have little relevance to amino acid sequence modification of the MTSP7 protease where they concern subtilisin amino acid sequence modification because subtilisins are secreted monodomain proteases suited for function in the soil outside a bacterium or fungus that secretes them. If the prior art modifications of subtilisin amino acid sequences were relevant to modification of the disclosed MTSP7 serine protease amino acid sequence set forth in SEQ ID NO:16, Pearson et al. would not have concluded, see page 326, left column, that while trypsin-like proteases and "[t]he subtilisin-like proteases[10] use exactly the same catalytic triad

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[9] Cheah et al., page 7185, right column. Three of the other four substitutions that Cheah et al. made at positions away from the catalytic triad also destroyed proteolytic activity and the fourth, "severely impaired activity", page 7186, right column. Cheah et al. conclude that a better understanding of the function, rather than dysfunction, of the viral protease must combine their mutagenesis "together with x-ray crystal structure data". Id.

[10] The initial diagnostic for the subtilisin serine proteases is the different order of the catalytic triad residues in their primary structure, Asp32 -> His64 -> Ser221, see, e.g., Table 1 of Bryan,

the families are non-homologous with very different three-dimensional structures". No subtilisin appears in Figure 2 of Pearson, indeed only the trypsin-like microbial protease of Bachovchin et al. appears in Figure 2 of Pearson, with a very low similarity score. The earliest report of site-directed mutagenesis of a subtilisin reviewed by Bryan, a single amino acid substitution made by Thomas et al., 1985, reference number 168, left column at page 221, was informed by the earlier X-ray diffraction analyses of subtilisin crystals, Wright et al., 1969, made of record herewith.

The artisan looking to the specification to see whether or not Applicant possessed myriad combinations of as many as 23, or 44, or 88 alterations in amino acid sequences of SEQ IDs NOs:16 or 18 would conclude that the necessary indicia are absent because: The specification identifies functions for amino acids at only sixteen positions, both the Response and the publications cited therein agree that the three amino acids constituting the catalytic triad cannot be changed and the specification teaches away from altering six other positions and, the specification does not set forth the boundaries or constituents of either an oxyanion hole or the boundaries or constituents of any other feature of the protease other than an activation cleavage site. "While one does not

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2000, using BPN' enumeration, which is distinct from the order of catalytic triad residues in the trypsin-like serine proteases, His -> Asp -> Ser, see Figure 3 of Cheah et al. The Response cites Wells et al., an early disclosure of altering the amino acid sequence of the secreted subtilisin BPN' of *Bacillus amyloliquefaciens*, used a three-dimensional model constructed with data supplied by X-ray diffraction studies of crystals of subtilisin BPN', see Figure 1, to identify two amino acids of the mature protease for modification: one position with uncharged substitutions at the other position with charged and uncharged substitutions, see Table 1. The Response also cites Carter et al., another early report of subtilisin BPN' modification, describe alanine substitutions at single positions of the catalytic triad that cripple proteolysis and multiple alanine substitutions at two, or all, of the triad positions that all but abolish proteolysis, see k_{cat} columns of Tables 1 & 2. Their remaining substitution, S24C, was made to attach the protease to a sepharose column, and all substitutions and the structures they depict in Figure 3 were informed, p. 568, right column, by X-ray diffraction studies of subtilisin BPN' crystals. Atwell et al., 1999, discuss alteration of a previously-altered *Bacillus amyloliquefaciens* subtilisin BPN' catalytic domain but found that, first page, right column, "[a]s expected, the active site residues, including the catalytic triad and oxyanion hole, were completely conserved in the selection" because only the absence of alteration could ensure detectable proteolytic activity.

need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Indeed the specification suggests no teaching or motivation for altering features of the MTSP7 protease beyond the activation cleavage site and an unpaired cysteine in the catalytic domain and fails to otherwise disclose or suggest the nature or source of the generic proteins of the rejected claims. The rejection of record is maintained because the artisan cannot envision other amino acid sequence alterations that Applicant might have contemplated capturing with the rejected claims, neither where the other alterations occur nor what any alteration might be.

Claim Rejections - New Matter and Written Description- 35 USC § 112

Claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67 and 69-72 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, because while the specification is enabling for,

> (i) a polypeptide capable of cleaving the artificial substrate S-2366, which may be a fusion polypeptide, comprising the MTSP7 protease catalytic domain having the amino acid sequence of SEQ ID NO:18,
>
> (ii) a protease capable of cleaving the artificial substrate S-2366 comprising the amino acid sequence set forth in SEQ ID NO:16 as well as its activated two-chain form,
>
> (iii) a protease capable of cleaving the artificial substrate S-2366 consisting of the MTSP7 protease catalytic domain with the amino acid sequence set forth in SEQ ID NO:18,
>
> (v) a variant of proteases of clauses (i)-(iii) having one or more amino acid substitutions of a free cysteine in the protease domain or an amino acid at positions 205-209 of SEQ ID NO:15, and,
>
> (vi) conjugates comprising same, solid supports attached to same, and assay methods utilizing same,

is not enabling for any embodiment of a polypeptide comprising a MTSP7 protease catalytic domain having an amino acid sequence diverging from the sequence of SEQ ID NO:18 at as many as 23 amino acid positions or a polypeptide comprising a MTSP7 protease having an amino acid sequence diverging from the sequence of SEQ ID NO:16 at as many as 44 amino acid positions, for conjugates comprising same, solid supports attached to same, and methods of screening for modulators of protease activity comprising same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments at pages 27-35 of the Response filed 9 February 2005 have been fully considered but are not persuasive. In view of the preceding analysis of the issue of written description, clause (v) of the former rejection statement above has been modified. Arguments presented in the Response take up the factors of the *Wands* analysis,[11] focusing particularly on issues of undue experimentation and unpredictability. The analysis of the breadth of the rejected claims relative to the paucity of teachings in the specification is set forth at pages 6-8 above; reviewing the functional roles of sixteen amino acids identified in the specification which teaches that only seven of the sixteen may be altered without loss of MTSP7 function, is taken as before. The rejected claims do not reach single substitutions at any of 44 identified positions. Instead, given the most limited construction of their scope, the claims reach arbitrary allocations of any or all of amino acid substitutions, additions, or deletions, in any combination or pattern, at as many as 44 positions anywhere in the remaining 422 amino acid positions in SEQ ID NO:16, or 88 positions in the case of claim 121, or at as many as 23 positions anywhere in the remaining 229 amino acid positions in SEQ ID NO:18. The Response admits, and the prior art confirms. that amino acids of the catalytic triad must not be altered, and the specification teaches that only a seventh, unpaired, cysteine can be substituted in the catalytic domain, because, as one of skill in the art would recognize, altering the other six cysteines that the specification identifies within SEQ ID NO:18 could disrupt the catalytic domain's tertiary structure.

The Response suggests that "existing crystal structures, structural comparisons and structural similarities" of members of diverse groups within the broad serine protease family might inform alterations of SEQ ID NO:16, and its included SEQ ID NO:18. The Response cites only one publication, Lu et al. discussed above, describing the crystal

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[11] *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

structure of a Type II transmembrane serine protease having a substantial relationship to the MTSP7 protease available to one of skill in the art at the time the invention was made. As noted above, Lu et al. show that substitutions can be made at five positions to alter the enterokinase proteolytic activity but that could not be predicted to sustain its activity in advance, even though they had determined the tertiary structure of the enteropeptidase protease domain by X-ray diffraction analysis of enteropeptidase crystals. Lu et al. also indicate, left column, page 369, that their findings are not likely to be predictably applied to "other serine protease that participate in highly-regulated metabolic pathways." The Response cannot explain how the distantly-related structures of the secreted, chymotrypsin-like, subtilisins, often modified to make them even more stable in destabilizing industrial applications, can inform any meaningful alteration of a Type II transmembrane serine protease such as the disclosed MTSP7 protease. Page 30 of the Response proposes that published "methods and guidance for comparing amino acid sequences to generate and confirm sequences" would permit one of skill in the art to redesign the disclosed MTSP7 protease to generate the myriad species embraced by the claims, yet the articles cited for that proposition concern comparisons of amino acid sequences found in Nature, rather than design of amino acid sequences.

The Response suggests at pages 30-31 that methods of assaying serine protease activity might mitigate the absence of publications disclosing tertiary structures of other mammalian Type II serine proteases, and that combining assays for protease activity with the specification's exemplification of the substitution of an amino acid for a cysteine that the specification identifies as unnecessary can somehow guide the artisan to make multiple alterations of as many as 44 of the 422 amino acids the specification ignores in SEQ ID NO:16. The Response suggests, pages 31-32, that useful alteration of the MTSP7 polypeptide is predictable in view of the specification's (1) "exemplary

polypeptides", but the specification discloses only a single MTSP7 polypeptide, (2) identification of "key regions and residues that one of skill in the art would know to conserve", yet the specification teaches only nine amino acid positions in the 438-amino acid sequence of SEQ ID NO:16 that must be conserved, and (3) provision "of reference points for alignments with [the sequences of] other known serine proteases", yet the specification discloses only three amino acid positions, the catalytic triad, that permit the artisan to recognize the MTSP7 protease as a trypsin-like serine protease, providing no teaching that any of the 435 other amino acids in SEQ ID NO:16 are useful for any particular alignment and teaching that only six of the 435 other amino acids may be changed for a disclosed purpose. The specification teaches no relationship between a useful prior art alteration at an amino acid position in the amino acid sequence of trypsin, or a trypsin-like serine protease, nor does it teach any correspondence between positions in the MTSP7 protease amino acid sequence, apart from the catalytic triad, and positions in amino acid sequences of any other trypsin-like protease, including other Type II transmembrane serine proteases.

With regard to enablement based on assay, the specification discloses only a generic substrate for a generic protease activity because the only disclosed substrate, the S2366 peptide, will also serve as a substrate for structurally-distant proteases. With regard to whether "undue" experimentation is needed to fill the gap between the six positions taught to be suitable for modification, and the myriad combinations of multiple substitutions at the 422 other positions in SEQ ID NO:18 that the specification ignores, the standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a **reasonable correlation** must exist between the scope asserted in the claimed subject

matter and the scope of guidance the specification provides.[12] The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*.[13] The citation of Cheah et al. at page 33 of the Response does not support the proposition that producing useful protease variants by making amino acid sequence alterations at as many as 23, or 44, undisclosed positions outside of the catalytic triad requires no undue experimentation. This is because six amino acid substitutions that Cheah et al. made at positions highly conserved among picornavirus proteases, each of which had an algorithm-based correspondence to a position in the trypsin amino acid sequence, abolished the activity of the rhinovirus 3C protease and the remaining substitution they made at a seventh conserved protease amino acid position severely impaired its proteolytic activity. Eradicating protease activity is not evidence that protease activity is predictably retained when modification is guided by algorithm-based similarity.

Without specifically citing any instance of concurrent multiple substitutions in any of the 575 documents supplied to date in Information Disclosure Statements, at pages 33-34 the Response alleges that "evidence" of "numerous mutations" in diverse members of "the larger family of serine proteases" provides both guidance and predictability in making multiple, concurrent, mutations in a single serine protease such as the disclosed MTSP7 protease, "using structure-function correlations". The Response thus implies that different amino acid sequence modifications reported in different serine proteases may be usefully imported into the MTSP7 serine protease on the basis of an algorithm-driven similarity even though no other single protease need be shown to have sustained all of the amino acid sequence modifications available for importation, and indeed no two proteases need be shown to have sustained a single corresponding amino acid sequence modification that might be imported into the disclosed MTSP7 protease, in

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[12] *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (emphasis supplied).
[13] 42 USPQ2d 1001 (Fed. Cir. 1997).

order to reach the degree of divergence permitted by the rejected claims. Except for the activation cleavage site and an unpaired cysteine, the specification itself fails to indicate where an amino acid sequence modification can be imported. In view of the request in the Response for documentation showing that "making multiple substitutions in serine proteases would be unpredictable", a review of the rejection of record at pages 9-12 of the Office communication mailed 9 September 2004 shows that its analysis of the *Wands* factors indicated that

> "**unpredictability** exists in the art where no members of the class of human serine proteases having domains that correspond to the MTSP7 protease catalytic domain set forth in SEQ ID NO:18 have had as many as 23 amino acids specifically identified for concurrent modification".

In this regard, Cheah et al., cited in the Response, show that it is not predictable to make a functional protease by separately making single amino acid substitutions at positions not part of a catalytic triad but analogous, based on a sequence comparison algorithm, to positions in trypsin that are not part of the catalytic triad. It is logical to conclude that making a set of the amino acid substitutions at positions corresponding to those used by Cheah et al. is even less likely to provide a functioning protease. The conclusion of "unpredictability" made in the Office communication of 9 September 2004, and sustained herein, does not concern serine proteases generally but is instead limited to members of the relevant class of serine proteases with "domains that correspond to the MTSP7 protease catalytic domain set forth in SEQ ID NO:18", i.e. the class of Type II transmembrane serine proteases such as the hepsin, endotheliase 1, matriptase and MTSP7 proteases. This is because no publication of record indicates that a Type II transmembrane serine protease has yet been modified by importing multiple concurrent, modifications of as many as 23 amino acid positions, or even a few amino acid positions, from a either a member of this same class of serine proteases or a member of

another class of serine proteases where the publications of record concerning such proteases either fail to propose any particular modifications or, as in Example 2 of the instant application, make only one. Although not assayed for proteolytic activity, the C313S-modified MTSP7 protease of Example 2 of the instant application need not be, and is considered to provide a functioning MTSP7 protease variant, because there is no reason to believe that it lacks protease activity.

The Response suggests at page 34 that a review by Bryan, 2000, might inform the alteration of amino acid sequences of SEQ IDs NOs:16 and 18 in listing subtilisin amino acid sequence modifications wherein substituents are reported for over 50% of the amino acid positions in the mature protease and argues that focusing on incremental progress in modifying this secreted monodomain protease over the past 25 years, where the first X-ray diffraction analysis of crystallized subtilisin was reported over 35 years ago,[14] ignores "a large collection of structure-function data" available "for a serine protease" at the time Applicant's priority document was filed. Close reading of the article will show that particular modifications were imported to another subtilisin from the subtilisin where they were originally made but the scope of claims rejected for lack of enablement herein reaches 10% divergence in the amino acid sequence of Type II transmembrane serine protease. Bryan does not suggests that modifications made in any subtilisin might be imported to a trypsin-like serine protease and those instances of concurrent, multiple, amino acid modifications in a single subtilisin protease that Bryan discusses, see sections 2.1.1. through 2.2.2. and 2.2.4., at pages 204-212 and 213-214, involve stability-altering modifications at either or both of a subtilisin's surface calcium binding sites, structural features not found in Type II transmembrane serine proteases, linked to other modifications elsewhere. As noted above, all subtilisin modifications are

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[14] Wright et al., 1969, Nature Vol. 221, pages 235-242, made of record herewith.

informed by or, when produced by "random mutagenesis", confirmed by knowledge of the tertiary structures of subtilisins obtained by X-ray diffraction analysis of subtilisin crystals. The specification provides no such guidance for the MTSP7 protease.

The Response also reiterates the argument that combining the claims' recitations of a desired result, 80% identity or 90% identity plus catalytic ability, with identification in the specification of (1) three positions of the catalytic triad in the amino acid sequences of SEQ IDs NOs:16 and 18 that must be left unchanged, (2) a proposed activation cleavage site, and (3) a cysteine in the amino acid sequence of SEQ ID NO:16, are sufficient for enablement. The specification provides no guidance, and the closest art of record provides no guidance, for such extensive alterations that result in a functioning protease. Even if combined with the publications cited at page 25 of the Response, the specification cannot support modification of 10%, or 20%, of amino acid positions in the sequence set forth in SEQ ID NO:18 where the prior art of record does not identify any positions in the enteropeptidase catalytic domain amino acid sequence, the closest of Type II transmembrane serine protease having a tertiary structure determined by Lu et al., , that can be altered yet permit retention of MTSP7 protease catalytic activity with the artificial peptide substrate S2366 disclosed in the specification or retention of the undisclosed, native, proteolytic activity of an MTSP7 protease having the amino acid sequence of SEQ ID NO:16. The rejection of record is therefore sustained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-6, 8-10, 18, 19, 50-55, 59-61, 65-67, 69-72 and 117-122 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments at pages 17-27 of the Response filed 9 February 2005 have been fully considered but are not persuasive. This communication is not made final

because the use of the transitional phrase "consisting essentially of" was not a basis for rejection of claim 4 in the rejection of record, and because the use of the term "serine protease activity" was not a basis for a rejection of record of any claim herein.

The amendments of 9 February 2005 to the preamble of claim 4 and clause (c) therein do not resolve the problems of indefinite description that arise from repeating the term "portion" and the new problem that arises from reciting "only portion". Claim 4, and claims 6, 52-55, 69, 117 and 118 depending therefrom, are indefinite primarily because no "portion" of a polypeptide of claim 4 knows from whence it came, where designations of proteins in the specification and the prior art are arbitrary, and because the term "portion" has no definite boundaries where it may be a tripeptide, or a dipeptide, or even a single amino acid. Recitations of clauses (a)-(c) of claim 4 are circular, thus indefinite, in view of the definition at page 20 of the specification stating that an "only MTSP7 portion" already "consists essentially of' of two different entities, that which is a protease domain and that which is a "portion" of it. Claim 4 is further indefinite in reciting the transitional term "consisting essentially of" in clauses (a) and (b) because the claim describes a single molecule which, unlike a composition of matter having at least two components wherein one is the predominant component, has no physically separate, lesser, component thus cannot "consist essentially of" one component. Appropriate transitional terms in this situation are "comprises", "has", and "consists of".

Clause (c) of claim 4 independently renders the claim indefinite because it cannot be a distinguishable alternative to clauses (a) and (b), thus has no meaning in referring to clauses (a) and (b). Specifically, a MTSP7 portion of clause (a) that is "a polypeptide consisting essentially of . . ." cannot become "a catalytically active portion" of itself and a MTSP7 portion of clause (b) that has 99% to 90% identity with SEQ ID NO:18 due to a deletion of amino acids and is still a protease is already a "catalytically active portion" of

itself. Claims 6, 52-55, 69, 117 and 118 are included in this rejection because they depend from claim 4 but do not otherwise resolve its indefinite description. This rejection is best addressed by amending claim 14 to either restate "a portion" based on a specific disclosure in the specification or to delete all references to "a portion" in rewriting the claim, and also by deleting the inappropriate transitional phrase "consisting essentially of" from the claim.

In a new basis for rejection, claims 1, 2, 4-6, 8-10, 18, 19, 50-55, 59-61, 65-67, 69-72 and 117-122 are indefinite because claims 1, 4 and 119-121 recite "serine protease activity", affecting claims 2, 5, 6, 8-10, 18, 19, 50-55, 59-61, 65-67, 69-72, 117 and 118 that depend from claims 1 and 4. The term "serine protease activity" is ambiguous, thus indefinite, because it fails to define the nature of the proteolytic activity described by the specification, which is a proteolytic activity with the peptide substrate S2366. A peptide may be cleaved by a variety of proteases, whether serine proteases, metalloproteases, or cysteine proteases, and the failure of the claims and the specification to identify what is intended by "serine protease activity" leaves the metes and bounds of the intended subject matter uncertain for the artisan and the public seeking to determine the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language.

Claims 4, 6, 52-55, 69, and 122 remain rejected for reasons of record, and claims, under 35 U.S.C. § 102(e)(1) as being anticipated by Alsobrook et al., US 2003/0170630, of record.

Applicant's arguments filed 9 February 2005 have been fully considered and are persuasive in establishing that Alsobrook et al. cannot have disclosed a substantially purified two-chain protease of claim 120 herein because Hooper et al. disclose that auto-catalysis of the cleavage at the activation cleavage site produces a heterogeneous set of products. The Response filed 9 February 2005 is not, however, persuasive in establishing that the rejected claims 4, 6, 52-55, 69, and 122 avoid the disclosure by Alsobrook et al. of the human serine protease set forth in their SEQ ID NO:2. The Response filed 9 February 2005 suggests at pages 39-40 that the Amendment to the preamble of claim 4 now excludes the protease of Alsobrook et al. comprising a 420-amino acid sequence because that sequence actually has two or more "MTSP7 portions", where one "portion" is identical to the amino acid sequence of SEQ ID NO:18 and other "portions" that are "nearly or completely identical to portions of SEQ ID NO:18" occur at, e.g., "amino acids 79-100 and amino acids 142 to 182 of SEQ ID NO:2" of Alsobrook et al. The Response argues limitations that are not in the claim where clauses (a) and (b) therein have no provision linking identity of a reference amino acid sequence to that set forth in SEQ ID NO:18 with an absence of an amino acid sequence having identity to another reference amino acid sequence set forth in SEQ ID NO:18 or a "portion" thereof. Instead, as noted above, the amendment of claim 4 filed 9 February 2005 renders the claim more ambiguous than before. There is no clear basis in the specification for the exclusory nature of the amendment to the claim preamble and, because the meets and bounds of the phrase "a protease domain . . . consisting essentially of" cannot be structurally construed, when functionally construed it cannot be regarded to exclude another "portion" of the amino acid sequence of SEQ ID NO:2 of Alsobrook et al. where no other function is specified for another "portion" of an MTSP7 protease, which is an arbitrary designation. Claims 6, 52-55, and 69 are included in the

rejection of record of claim 4 for reasons of record because SEQ ID NO:2 of Alsobrook comprises the features recited in claim 6 and because Alsobrook et al. also disclose the preparation of conjugates comprising targeting agents linked to any of their disclosed proteins so as to permit attachment of the conjugate to a surface and its subsequent detection, meeting limitations of claims 52-55 herein, and because claim 69 herein describes a method disclosed by Alsobrook et al. for using a disclosed protein to screen test compounds in order to detect modulators of the activity of the proteins. Claim 122 also remains rejected because the disclosure of SEQ ID NO:2 of Alsobrook et al. meets the limitations of the claim where the meets and bounds of "a protease domain . . . consisting essentially of" cannot be structurally construed, and when functionally construed cannot be regarded to exclude the amino acid sequence of SEQ ID NO:2 of Alsobrook et al. which meets the functional limitation in having protease activity and no other particular activity that is either essential or non-essential.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
28 April 2005

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600